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Clinical Impact of Updated Diagnostic and Research Criteria for Alzheimer's Disease

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The most common form of disabling cognitive impairment in older people, Alzheimer's disease (AD) dementia currently affects an estimated 5.4 million Americans.¹ By 2050, AD dementia is projected to affect more than 13.5 million older US adults.² According to the World Alzheimer's Report,³ the number of afflicted people and the associated costs of AD are projected to skyrocket around the world due to the growing number of people living to older ages.

To help clinicians recognize and diagnose AD, work groups for the NINCDS and the ADRDA (better known as the Alzheimer's Association) developed diagnostic criteria⁴ in 1984, which have remained unchanged until now. At that time, AD was considered a discrete clinicopathological entity, requiring evidence of dementia and likely or confirmed evidence of moderate-to-severe AD neuropathology.⁵ Due to advances in AD research in the past 27 years, it is now recognized that AD develops in phases, such that the pathology begins long before the patient exhibits symptoms. The NIA and the Alzheimer's Association have recently updated the criteria to address: preclinical AD,⁶ MCI due to AD,⁷ and dementia due to AD.⁸ While the new criteria for MCI due to AD and for dementia due to AD are to be used for clinical diagnosis, the criteria for identifying preclinical AD are to be used only in research settings.

Revising the Original Criteria for AD

The original criteria had several limitations that the NIA/Alzheimer's Association addressed in the updated criteria. For example, the original criteria lacked recognition of potential causes of dementia other than AD, such as dementia with Lewy bodies, frontotemporal dementia, and vascular dementia.

Additionally, the new criteria introduce the concept that AD progresses over time and manifests across a continuum. This neurodegenerative disorder may begin 10 or more years before patients present with symptoms of dementia. Further, this reconceptualization acknowledges that dementia does not comprise the entire AD pathology, but rather that people gradually progress from the preclinical stage of AD to MCI to dementia. Although, it is not yet known whether everyone with preclinical biomarker evidence of AD pathophysiology progresses to the clinical phases of the illness. AD pathology may eventually be detected in its asymptomatic or prodromal stages via biomarker evidence.

Biomarkers essentially did not exist almost 30 years ago when the original criteria were written; neuroimaging was primarily used to rule out other diagnostic entities rather than used as a measure of the disease itself. Using biomarkers in research may help to elucidate the underlying pathology of clinical symptoms, which can hopefully lead to early identification of and preventive treatment for patients with preclinical AD.

Biomarkers in Assessment of AD Pathology

A key problem in using biomarkers is applying them in the diagnosis of AD. In the research setting, neurologic evidence of early AD pathology can now be detected *in vivo* in patients who are clinically normal. Also, research⁹ using MRI scans, FDG PET scans, and CSF assays has shown that many patients with MCI have biomarker levels that fall between those of normal aging and those of dementia.

A research opportunity exists for conducting longitudinal follow-up studies that track changes in biomarkers and to further link them to a person's subsequent clinical course of AD neuropathology. While there is more to learn about these biomarkers before they are routinely recommended in the clinical setting, a PET technique for detecting the accumulation of amyloid plaques in the brain may receive FDA-approval soon, pending the development of training procedures for clinicians to reliably interpret the results.

Overall, the use of biomarkers is in a stage of evolution, and measurement to distinguish normal states from diseased states are not yet standardized for clinical use. Community studies are needed to determine how to use biomarkers in real-world settings and to obtain generalizable and replicable results. Therefore, at this time, the consensus groups for the NIA/Alzheimer's Association criteria stressed that the primary use of biomarkers should be in research settings. In the meantime, becoming familiar with potential biomarkers would be advantageous for clinicians.

Cognitive Tests in MCI Assessment

Even while the role of biomarkers and genetic testing in the clinical setting continue to be clarified, clinicians do have tools available to assess patients for MCI due to AD. Memory impairment is central to most clinical presentations along the AD spectrum, and clinicians need to use some form of memory assessment. To truly assess memory, several items should be listed followed by cognitive activities and a substantial delay (eg, 10–30 minutes) before asking patients to recall the listed items. This allows patients more time to forget the items if they are going to do so, a cardinal symptom present early in the development of AD. To evaluate patients, the MCI due to AD work group recommended that clinicians use an assessment tool, such as the following:

- Free and Cued Selective Reminding Test (memory)
- Rey Auditory Verbal Learning Test (memory)
- California Verbal Learning Test (memory)
- Logical Memory subtest of the Wechsler Memory Scale Revised (memory)
- Visual Reproduction subtest of the Wechsler Memory Scale Revised (memory)
- Trail Making Test (executive function)
- Letter and Category Fluency of the Boston Naming Test (language)

If formal tests such as these are not available, informal techniques may be used. However, informal tests may not be sensitive enough to detect subtle impairments in patients with early MCI. Additionally, because patients are often impaired in several domains besides memory, multiple tests may need to be conducted to obtain a thorough and accurate clinical assessment.

Revising the *DSM-5* Criteria

The APA is currently revising the *DSM* criteria,¹⁰ including those for AD. The category has been renamed “Neurocognitive Disorders” to replace the current, more cumbersome category “Delirium, Dementia, Amnesic, and Other Cognitive Disorders.” The new subcategories are *mild neurocognitive disorder*, which is comparable to MCI, and *major neurocognitive disorder*, which is consistent with dementia; both will have criteria for being “associated with AD.” The APA work group is currently rewording its former draft of the criteria for these etiologic subtypes of mild and major neurocognitive disorders to harmonize them with the new NIA/Alzheimer's Association criteria described here. However, the terminology will differ somewhat because of the *DSM's* broader mandate and various audiences. Currently, field testing is being conducted with the proposed mild and major neurocognitive disorder criteria. The *DSM-5* is slated to be published in 2013.

Future Directions in AD Research

AD biomarker research will have increasing roles to play in the scientific study and diagnosis of AD and in the evaluation of AD-modifying treatments. A majority of previous treatment trials have been conducted in patients with dementia due to AD, and there is a

concern that some of these treatments may be initiated too late to have the most profound benefit. A much smaller number of studies have been conducted in patients with MCI, most recently using biomarker evidence of amyloid-beta pathology to support the diagnosis of AD. The new NIA/Alzheimer's Association criteria anticipate the performance of more trials in the earlier clinical and preclinical stages of AD. There is reason to believe that PET (when approved by the FDA) and CSF measurements of amyloid pathology could be used to help rule out the diagnosis of AD (if the biomarker tests are negative) and perhaps improve confidence in the diagnosis of AD (if the tests are positive). However, experts note the need for further studies to help confirm that previous findings are generalizable to the community setting and in the oldest old (who have been less well studied and who may be different in several important respects), to clarify the extent to which the different biomarkers could be used alone or in combination to better predict a person's clinical course, and to help establish the reliable image acquisition, analysis, and interpretation procedures needed to optimize their role in the clinical setting.

For Clinical Use

- Researchers have reconceptualized AD as a progressive sequence of biological changes, which begin before the onset of symptoms and roughly correspond to the preclinical and increasingly severe clinical stages of the disorder
- While the NIA/Alzheimer's Association clinical diagnostic criteria for MCI due to AD and dementia due to AD may have their most useful role in the research setting; *DSM-5* criteria are expected to be incorporate several similar features
- Become familiar with the tools with which biomarkers and susceptibility genes can be detected, their emerging role in the evaluation of disease-modifying and preclinical treatments, and the roles they are ultimately anticipated to play in the clinical setting
- Use an assessment tool to evaluate patients for cognitive impairments

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Abbreviations

AD	Alzheimer's disease
ADRDA	Alzheimer's Disease and Related Disorders Association
APA	American Psychiatric Association
CSF	cerebrospinal fluid
DSM-5	<i>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</i>
FDG PET	fluorodeoxyglucose positron emission tomography
MCI	mild cognitive impairment
NIA	National Institute on Aging
MRI	magnetic resonance imaging
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke